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Therapeutic potential of histamine H₃ receptor agonists and antagonists

Rob Leurs, Patrizio Blandina, Clark Tedford and Henk Timmerman

The histamine H₃ receptor was discovered 15 years ago, and many potent and selective H₃ receptor agonists and antagonists have since been developed. Currently, much attention is being focused on the therapeutic potential of H₃ receptor ligands. In this review, Rob Leurs, Patrizio Blandina, Clark Tedford and Henk Timmerman describe the available H₃ receptor agonists and antagonists and their effects in a variety of pharmacological models *in vitro* and *in vivo*. The possible therapeutic applications of the various compounds are discussed.

Histamine mediates its action via three distinct receptor subtypes, H₁, H₂ and H₃ (Refs 1, 2). The subclassification of the histamine receptors by the pioneering work of Ash and Schild³, Black *et al.*⁴ and Arrang *et al.*⁵ has been supported by recent molecular biological approaches^{1,2}. The demonstration of the existence of both H₁ and H₂ receptors opened important new avenues for successful treatment of allergic conditions (H₁ receptor antagonists) and gastric ulcers (H₂ receptor antagonists). Although considerable progress has been made in the medicinal chemistry of H₃ receptor ligands and the understanding of

the role of the H₃ receptor in (patho)physiology, no H₃ receptor-related drugs have yet been introduced.

The H₃ receptor was discovered originally on histamine-containing neurones as a presynaptic receptor regulating the release and synthesis of histamine⁵ (Box 1). In the mammalian brain, histamine-containing cell bodies are located in the tuberomammillary nucleus of the posterior hypothalamus and project to most cerebral areas^{6,7}, indicating that H₃ receptor ligands can potentially affect a variety of brain functions. Moreover, H₃ receptors not only act as autoreceptors, but are also involved in the presynaptic regulation of the release of acetylcholine, dopamine, GABA, glutamate, noradrenaline and 5-HT (Box 1). Recent data show that H₃ receptors are not confined to the brain, but also play a modulatory role in peripheral neurotransmission (e.g. in the gastrointestinal tract, the cardiovascular system and the airways)^{1,2,8,9}.

Selective H₃ receptor agonists and antagonists

Since the initial discovery of the H₃ receptor in 1983 (Ref. 5), major progress in the development of H₃ receptor agonists and antagonists has been made. Several potent and selective agonists are currently available^{10,11}. Methylation of the α-carbon atom of the ethylamine side-chain of histamine leads to the potent H₃ receptor agonist R-(α)-methylhistamine (Fig. 1). In combination with its less active s-isomer, this compound has been very useful for the pharmacological characterization of H₃ receptor-mediated effects¹⁰. Further H₃ agonists are produced if the amine function of histamine is replaced by an isothiourea group (inetit), an amidine moiety (SKF91606) or incorporated in a ring structure (immezipip) (Fig. 1)¹²⁻¹⁵. Because of its early availability, R-(α)-methylhistamine has been used extensively *in vitro* and *in vivo*. Recently, high affinity of R-(α)-methylhistamine for the histamine-metabolizing enzyme histamine-N-methyltransferase was observed¹⁶.

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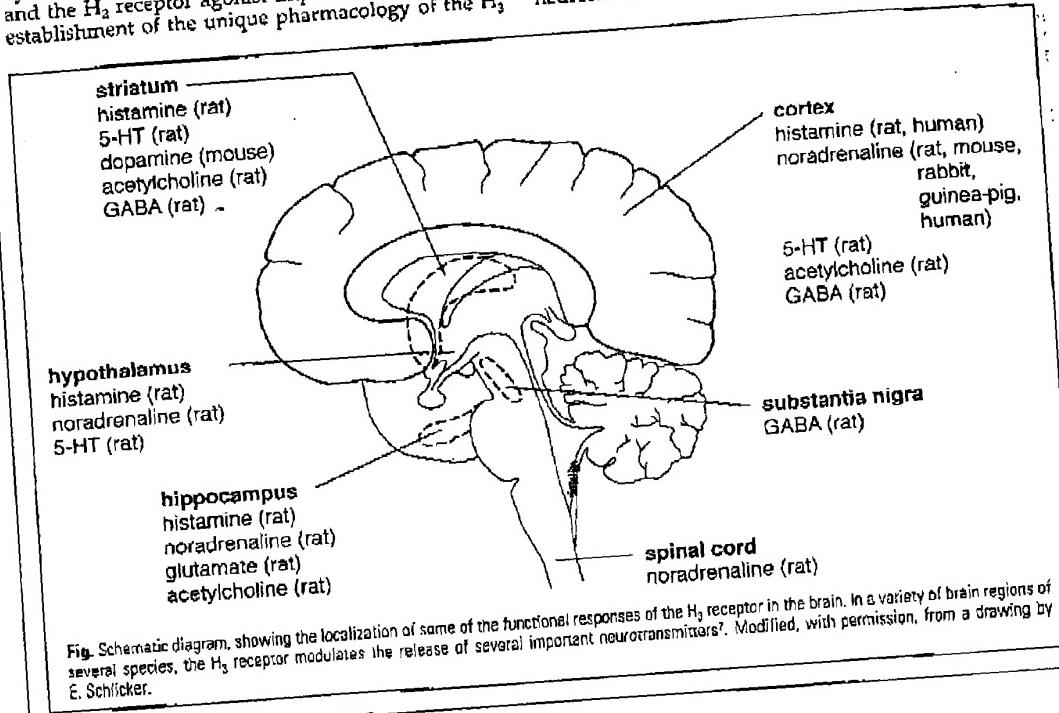
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Box 1. Modulation of CNS neurotransmission

In 1983, Arrang *et al.*¹ described a new histamine receptor subtype that modulated the K⁺-evoked release of [³H]histamine from cerebral cortex slices preloaded with [³H]-L-histidine. This histamine H₃ autoreceptor was stimulated by low concentrations of histamine, insensitive to selective H₁ and H₂ receptor agonists, and the inhibition by histamine was antagonized by both the H₂ receptor antagonist burimamide and the H₂ receptor agonist imipramidine². After the establishment of the unique pharmacology of the H₃,

autoreceptor, its presence was detected in several other brain areas^{2,3} (Fig.), including the human cerebral cortex⁴. The persistence of H₃ receptor effects in the presence of tetrodotoxin and experiments with synaptosomes indicate the presynaptic location of the H₃ autoreceptor⁵. Histamine exerts a tonic influence on presynaptic H₃ receptors both *in vitro* and *in vivo*^{2,3}. Consequently, systemic administration of H₃ receptor agonists and antagonists reduces and increases neuronal histamine release, respectively, leading to



Methylation of the imidazole ring of R-(α)-methylhistamine by histamine-N-methyltransferase results in a very short plasma half-life in humans (3 min), which, combined with the high polarity of R-(α)-methylhistamine, strongly limits its brain penetration. With the development of a series of R-(α)-methylhistamine prodrugs (Fig. 1), the latter problem of penetration is largely eliminated¹⁷. The azomethine group in BP294 (Fig. 1) prevents the methylation of the imidazole ring by histamine-N-methyltransferase and improves oral bioavailability. In humans, a single oral dose produces long-lasting (>24 h) plasma levels of both BP294 and R-(α)-methylhistamine (after non-enzymatic cleavage in blood plasma)¹⁶. Moreover, selective substitution of the azomethine group allows substantial brain penetration [e.g. FUB307 (Fig. 1)]¹⁸.

Many potent H₃ receptor antagonists have also been developed. The prototypic H₃ receptor antagonist, thioperamide (Fig. 2)¹⁹, has a nanomolar affinity for the H₃ receptor and penetrates fairly well into the brain. Despite

its widespread use, caution should be taken since thioperamide also has some affinity for the 5-HT₃ receptor²⁰ and probably interacts with neuronal GABA transport²¹. Replacement of the thiourea side-chain of thioperamide has led to a wide variety of H₃ receptor antagonists^{10,11}. Incorporation of an isothiourea moiety in the side-chain gives the highly potent H₃ receptor antagonist clobenpropit (Fig. 2), which was developed as a N-substituted derivative of imetit¹⁴. This antagonist is tenfold more potent than thioperamide *in vitro*, but has a reduced brain penetration. To increase central effectiveness and to overcome potential toxicological problems connected with the thiourea and isothiourea moieties, these groups have been replaced by several side-chains with other polar groups (e.g. ureas, amines, amides, ethers, carbamates and oxadiazoles) to produce the H₃ receptor antagonists FUB181, GR175737, GT2016 and UCL1199 (Fig. 2)¹¹. Many of these ligands show an improved brain penetration and high effectiveness *in vivo* in rodents. Particularly remarkable is the recent

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by histamine H₃ receptors

increased and decreased histamine levels in brain tissue, respectively². Microdialysis experiments that measure the release of endogenous histamine in the rat hypothalamus also indicate a tonic H₃ receptor-mediated inhibition at the autoreceptor⁵.

The development of the selective H₃ receptor agonist (R)- α -methylhistamine and antagonist thioperamide allowed the demonstration of the modulation of a variety of neurotransmitter systems via H₃ heteroreceptors. In the rat hypothalamus, H₃ receptors inhibit, for example, the release of 5-HT and noradrenaline⁶. Release of both these neurotransmitters is also reduced by presynaptic H₃ receptors in cerebral cortex slices of several other species⁷ (Fig.). Experiments *in vitro* show that H₃ receptor activation also inhibits the release of acetylcholine in the rat entorhinal cortex⁸, although a presynaptic localization of the H₃ receptor is unlikely as inhibition of K⁺-evoked release of [³H]acetylcholine from synaptosomes by H₃ receptor agonists was not detectable⁹. In mouse striatal tissue, dopamine release is affected by H₃ receptor activation¹⁰, and dopamine D₁ receptor-induced release of GABA from slices of rat striatum¹¹ and substantia nigra¹² is effectively inhibited by H₃ receptor activation on GABA-containing nerves. Finally, in a recent electrophysiological study using rat hippocampal slices, strong evidence for a presynaptic H₃ receptor-mediated regulation of glutamate release in the dentate gyrus was provided¹³.

Histamine H₃ receptor ligands do not substantially affect brain noradrenaline, dopamine or 5-HT levels *in vivo*¹⁴. Interestingly, acetylcholine release in both the rat hippocampus¹⁵, cerebral cortex¹⁶ and ventral striatum can be modulated by H₃ receptor ligands¹⁷. In the hippocampus, histamine, released from histamine-containing nerve terminals, stimulates acetylcholine release via H₂ receptors¹⁵. Interference with histamine-mediated neurotransmission via systemic administration of H₃ receptor agonists or antagonists decreases or increases the hippocampal acetylcholine release, respectively¹⁸. In the cerebral cortex of freely moving

rats, activation of postsynaptic H₃ receptors stimulates the release of GABA (Fig.), which, in turn, inhibits the depolarization-induced release of acetylcholine¹⁸. The reduced acetylcholine release in the cerebral cortex after systemic administration of H₃ receptor agonists is accompanied by an impaired performance of the rats in the object-recognition test and passive-avoidance response¹⁶.

These data show that the H₃ receptor is widely distributed throughout the CNS. This correlates well with autoradiographic studies¹⁹, which also indicate that the presence of H₃ receptors is not solely restricted to the histamine-containing neurones.

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development of GT2227 (Fig. 2). This H₃ receptor antagonist is active both *in vitro* and *in vivo*²², although a polar group is lacking in the side-chain. The high activity of this ligand suggests that the molecular architecture of the H₃ receptor is distinct from that of the H₁ and H₂ receptor.

Peripheral effects with therapeutic potential

The H₃ receptor can modulate a variety of functions of important peripheral organs. In cats, dogs and rabbits, but not in rats, H₃ receptor activation inhibits gastric acid secretion induced by food, pentagastrin or 2-deoxy-D-glucose⁹. This effect is secondary to the H₃ receptor-induced inhibition of the release of acetylcholine, histamine or somatostatin from vagal nerve endings, enterochromaffin-like (ECL) cells and D cells (somatostatin-releasing cells), respectively⁹. Because of the histamine tone in the stomach, H₃ receptor antagonists enhance gastric acid secretion induced by submaximal doses of 2-deoxy-D-glucose and pentagastrin⁹.

Despite its lack of effect on gastric acid secretion in the rat, R-(α)-methylhistamine (1–100 mg kg⁻¹ i.p.) shows a remarkable gastroprotective effect in this species. Gastric mucosal lesions induced by ethanol, aspirin or stress are inhibited effectively by R-(α)-methylhistamine, but this effect is only partially sensitive to thioperamide and clobenpropit, indicating that a non-H₃ receptor component is also involved⁹. The mechanism of protection seems to involve the mucosal layer, since histological studies show that R-(α)-methylhistamine increases the number of mucous granules in surface and neck cells and promotes rapid re-epithelialization⁹.

A role for H₃ receptors in the regulation of inflammatory processes has recently been found. In rodents, BP294 causes an inhibition of capsaicin-induced plasma extravasation and zymosan-induced paw swelling¹⁶. These effects are attributed to the expression of inhibitory H₃ receptors on sensory C fibres, which, in concert with histamine-releasing mast cells, act as a

negative-feedback system for the release of neuropeptides¹⁶. A similar feedback mechanism exists in the rat, guinea-pig and rabbit lung and in the rat dura mater, suggesting a beneficial effect of H₃ receptor agonists in neurogenic airway inflammation²³⁻²⁵ and also in migraine^{26,27}.

In the cardiovascular system, H₃ receptor activation has been reported to inhibit sympathetic neurotransmission in a variety of preparations⁸, including the human right atrium²⁸. In isolated guinea-pig hearts, H₃ receptor agonists reduce substantially the noradrenaline release in early myocardial ischaemia. Moreover, reperfusion-induced arrhythmias are inhibited by 50% by H₃ receptor stimulation²⁹. In the same preparation, H₃ receptor activation also inhibits the release of calcitonin-gene-related peptide (CGRP) from sensory C fibres³⁰. Since CGRP release is elevated in humans in severe conditions such as septic shock, heart failure and acute myocardial infarction, H₃ receptor agonists might be of therapeutic use in these conditions^{29,30}.

Sleep and wakefulness

The presence of histamine-containing cell bodies in the tuberomamillary nucleus of the posterior hypothalamus (an area involved in the maintenance of wakefulness) and their projections to the cerebral cortex suggest a role of histamine in the modulation of the arousal state and sleep-wake cycle. Lesions of the posterior hypothalamus are known to produce sleep in rats, cats and monkeys³¹, and neurochemical and electro-physiological studies indicate that the activity of histamine-containing neurones is maximal during periods of wakefulness and is suppressed by barbiturates and other hypnotics³². Intraventricular histamine induces the appearance of an arousing electroencephalogram (EEG) pattern in rabbits³³. Moreover, histamine release in the rat hypothalamus *in vivo* shows a circadian rhythm, with higher histamine release in periods with high locomotor activity³⁴. Conversely, inhibition of histidine decarboxylase has been shown to impair waking in rats³⁵. Strong evidence indicates that the effects of histamine on sleep parameters are mediated by the H₁ receptor, explaining the sedative side-effects of CNS-penetrating H₁ receptor antagonists³¹.

Modulation of histamine-mediated neurotransmission with H₃ receptor agonists [e.g. R-(α)-methylhistamine and BP294] results in an increase of the slow-wave sleep in rat and cats^{31,36,37}. Increased wakefulness, decreases in rapid eye movement (REM) and slow-wave sleep and increased locomotion are observed after systemic application of H₃ receptor antagonists³⁸⁻³⁸.

Cognition and memory processes

Dysfunctions of acetylcholine-mediated neurotransmission are considered to underlie the cognitive decline associated with ageing and Alzheimer's disease. However, changes typical of ageing and Alzheimer's disease occur within the context of alterations of other neurotransmitter

systems, including histamine^{39,40}. Histamine levels in the hypothalamus, hippocampus and temporal cortex have been found to be significantly lower in brains from patients with Alzheimer's disease compared with controls⁴⁰. Moreover, in Alzheimer's disease, the characteristic neurofibrillary tangles co-localize with histamine-containing neurones in the posterior hypothalamus⁴¹.

There is also direct evidence that histamine-mediated neurotransmission plays an important role in learning and memory. Histamine has been shown to influence synaptic plasticity in hippocampal slices⁴², and to increase recall in a step-down inhibitory avoidance task when given immediately post-training⁴³. Similarly, pre-testing administration of histamine enhances cognitive performance of rats in an active avoidance task while H₁ receptor antagonists impair memory retention^{44,45}.

Although histamine might affect cognition on its own, neurochemical studies suggest that histamine also modulates the activity of cholinergic neurons (Box 1). High levels of H₃ receptors are found in the frontal cortex and hippocampus, implying a role in higher learning function⁴⁶. Microdialysis studies show that activation of cortical H₃ receptors by local and systemic (5 mg kg⁻¹ s.c.) administration of imetit and R-(α)-methylhistamine reduces K⁺-evoked release of acetylcholine from the cortex of freely moving rats (Fig. 3)⁴⁷. The cognitive performance of rats in object recognition and a passive-avoidance response is strongly impaired by similar doses of these H₃ receptor agonists (Fig. 3)⁴⁷. Moreover, immezipim impairs performance in an olfactory social-memory test in rats⁴⁸. Conversely, a beneficial effect of R-(α)-methylhistamine has been reported in rodent spatial learning and memory, assessed using a water maze⁴⁹. Differences among the behavioural tests used may explain this discrepancy. Spatial learning is a primary function of the rodent hippocampus⁵⁰, while object recognition, passive-avoidance response and the olfactory social-memory test serve to measure a form of episodic memory, possibly localized in the frontal cortex. These responses are severely impaired by lesions of the basolateral system, which only slightly disturb water-maze performance⁵¹.

Studies with thioperamide and clobenpropit suggest that H₃ receptor antagonists may provide a novel approach to improve cognitive deficits. Thioperamide exerts procognitive activity in the olfactory social-memory test⁴, but other studies report that the procognitive effects of H₃ receptor antagonists only become fully evident when behavioural deficits are pronounced. Thioperamide improves significantly the response latency in a passive-avoidance response in senescence-accelerated mice, but is ineffective in normal-rate ageing mice⁵². Other studies report that administration of thioperamide (20 mg kg⁻¹ i.p.) or clobenpropit (20 mg kg⁻¹ i.p.) to mice impaired by scopolamine (1 mg kg⁻¹ i.p.) attenuates the amnesic effects of scopolamine in the elevated plus-maze test and the step-through passive-avoidance test^{53,54}.

R E V I E W

Attention-deficit hyperactive disorder

Attention-deficit hyperactivity disorder (ADHD) is a developmental disorder with underlying emotional, attentional and learning disabilities. The disorder has an onset in early childhood (there are approximately three million sufferers in the USA) and over 50% of those children diagnosed with ADHD will continue to experience attentional problems as adults⁵⁵. Underlying abnormalities in monoamine neurotransmitters appear to significantly contribute to the learning and motor disturbances in ADHD patients^{55,56}. The psychostimulants methylphenidate, dextroamphetamine and pemoline provide symptomatic relief but also produce several serious side-effects.

The use of H₃ receptor antagonists can be envisioned in attentional disorders on the basis of the previously described wake-promoting or vigilant profiles seen by EEG, the procognitive properties in animal models of learning and memory, and the direct effects on neurotransmitter release, particularly acetylcholine, noradrenaline and dopamine. Immature developmental models have been described in which impairments in cognitive processes or motor patterns are seen that are similar to those observed in ADHD (Refs 57, 58). In an immature rat model, pre-training administration of the selective H₃ receptor antagonist GT2016 was evaluated at doses (5–30 mg kg⁻¹ i.p.) that paralleled cortical H₃ receptor-occupancy profiles and enhanced cortical histamine release *in vivo*⁵⁹. GT2016 significantly improved the rate of acquisition in a multi-trial passive-avoidance-response task. Methylphenidate provided similar improvements in learning rates in immature rat pups^{60,61}. These data demonstrate that H₃ receptor antagonists may be of use in the treatment of ADHD. Not only do these drugs improve the cognitive deficits, but they also normalize motor disturbances⁶¹.

Epilepsy

Almost 50 years ago, the first clinical indications suggesting the involvement of central histamine-mediated neurotransmission in epilepsy were reported^{62,63}. In epileptic patients and healthy young children (especially of pre-school age), several brain-penetrating H₁ receptor antagonists occasionally induce convulsions^{62–64}. Moreover, direct H₁ receptor activation or modulation of CNS histamine levels by L-histidine loading, inhibition of histamine synthesis or metabolism in rodents has indicated that histamine may be an endogenous anticonvulsant⁶⁴. A role for the H₁ receptor in epilepsy is further supported by an increased H₁ receptor density (10–50%) in the focus of epileptic discharges in the temporal neocortex of nine patients with complex partial seizures, as measured by positron emission tomography (PET) studies with [¹¹C]doxepin⁶⁵.

As mentioned before, presynaptic control via the H₃ receptor is an important regulatory mechanism of histamine-mediated neurotransmission. Recent data indicate that various H₃ receptor antagonists (thioperamide, clobenpropit and AQ0145) decrease the seizure susceptibility of electrically induced convulsions in mice^{66–68} by

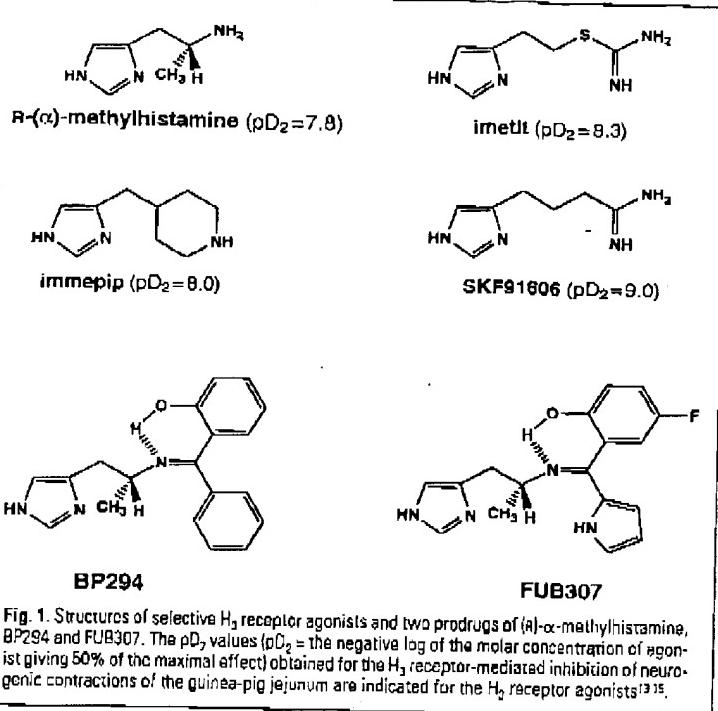


Fig. 1. Structures of selective H₃ receptor agonists and two prodrugs of (R)-α-methylhistamine, BP294 and FUB307. The pD_2 values ($pD_2 = \text{the negative log of the molar concentration of agonist giving 50\% of the maximal effect}$) obtained for the H₃ receptor-mediated inhibition of neurogenic contractions of the guinea-pig jejunum are indicated for the H₃ receptor agonists^{13,15}.

increasing endogenously released histamine in the brain. The anticonvulsant effect of these drugs is antagonized by pretreatment with H₃ receptor agonists or the H₁ receptor antagonist mepyramine^{66–68}. These findings support the anticonvulsive effect of endogenous histamine and suggest that H₃ receptor antagonists could represent a new approach to the development of antiepileptic drugs, especially in young children.

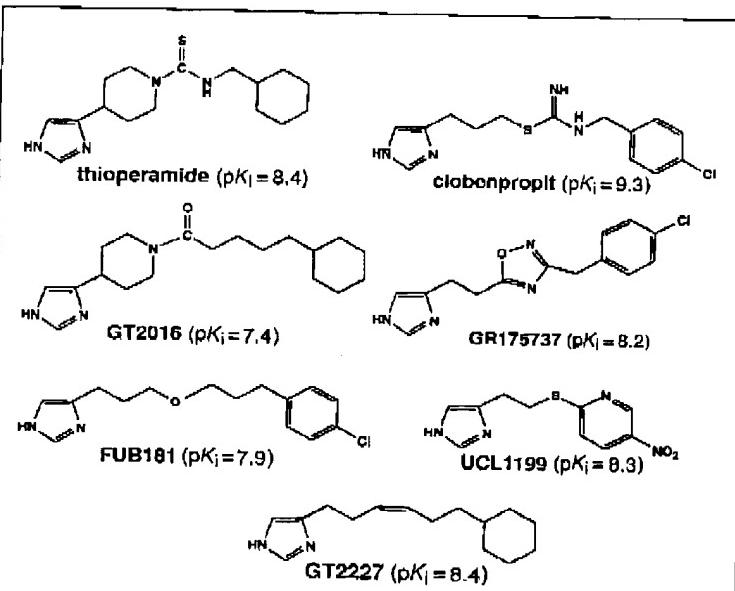


Fig. 2. Structures of selective H₃ receptor antagonists. The pK_i values are indicated¹¹.

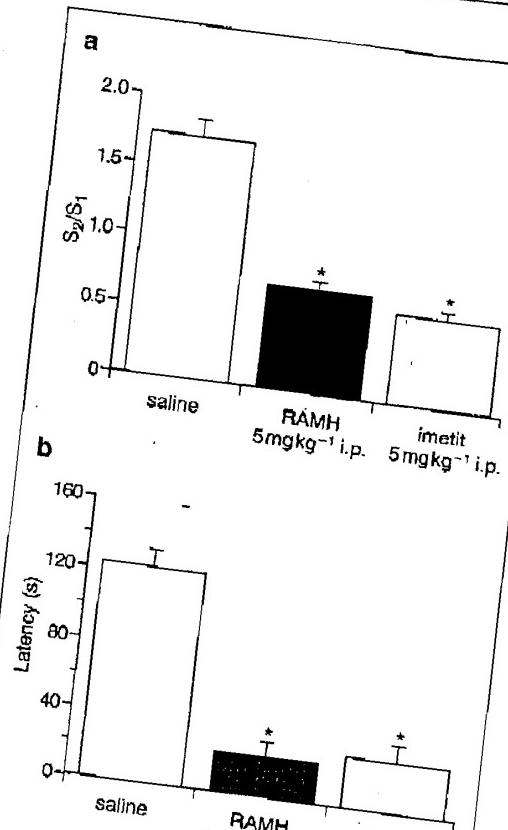


Fig. 3. Effects of systemic administration of the H_3 receptor agonists $(R)-\alpha$ -methylhistamine (RAMH) and imetit on: a: acetylcholine release in the cerebral cortex of freely moving rats as measured by microdialysis; and b: the cognitive performance in a passive-avoidance paradigm. The effects of the agonists on the acetylcholine release are expressed as the ratio S_2/S_1 , where S_1 and S_2 represent the K⁺-evoked acetylcholine release in two consecutive periods of stimulation. The agonists were administered before S_2 . * $P<0.05$ compared to saline administration. Modified from Ref. 47.

Obesity

Recently, the approval of dextroamphetamine by the Food and Drug Administration was met with great expectations for the treatment of morbid obesity. However, atrial valve problems observed in the 'fen/phen' (dexfenfluramine and phentermine) combination therapy have led to the removal of the product and have severely limited treatment options. Many new therapies under development for obesity are based on their action at the hypothalamic level (i.e. neuropeptide Y receptor antagonists, cholecystokinin receptor agonists, noradrenalin or 5-HT releasers and uptake inhibitors)⁶⁹.

A number of studies suggest that histamine can also suppress appetite and that histamine-containing neurones in the hypothalamus participate in the endogenous suppression of food intake. Intracerebroventricular injections of histamine depress feeding in rats, whereas

the application of H_3 receptor antagonists or depletion of endogenous histamine by inhibition of histidine decarboxylase elicits a feeding response⁷⁰. Moreover, chronic treatment of humans with CNS-penetrating H_3 receptor antagonists leads to weight gain. It is generally considered that histamine activates postsynaptic H_3 receptors in the ventromedial nucleus (VMH) (and possibly also the paraventricular nucleus) of the hypothalamus to suppress food intake⁷⁰. In addition, H_3 receptors have been identified with moderate density in the VMH (Ref. 46). In line with these observations, administration of thioperamide i.c.v. suppresses food intake, which is consistent with the drug-induced increase in histamine release in rats. This effect on appetite can be blocked by the concomitant administration of an H_3 receptor antagonist⁷⁰. In addition, the anorectic actions of both amylin and bombesin are mediated by the histamine transmitter system^{71,72}. Furthermore, dextroamphetamine increases histamine release in the rat hypothalamus, which potentially contributes to its anorectic effects⁷³. Recently, dysfunctions in histamine-mediated neurotransmission have been identified in the obese Zucker rat, a genetic model for obesity⁷⁴. The role of hypothalamic histamine in regulating body-weight homeostasis is thus very compelling, and supports the clinical use of H_3 receptor antagonists in the treatment of obese conditions.

Concluding remarks

Important progress has recently been made in the understanding of the role of the H_3 receptor. Clear indications for the potential therapeutic use of H_3 receptor agonists and antagonists are now available, and clinical trials are in progress or being planned. For H_3 receptor agonists especially, the feedback mechanism on sensory C fibres and resultant anti-inflammatory effects suggest a potential peripheral application in the treatment of asthma, migraine, cardiac disorders and inflammatory disorders, such as arthritis and bowel diseases. The potential for impairment of cognitive performance or the induction of sedation may restrict their use; thus, H_3 receptor agonists with limited accessibility to the CNS should be used in these indications. Currently, these hypotheses are being evaluated in clinical trials using BP294 (Ref. 16).

The CNS effects of the H_3 receptor antagonists make them interesting candidates for testing in several disorders of the CNS. These drugs show potential therapeutic effects in models of obesity and epilepsy. The observations that H_3 receptor antagonists have beneficial effects on learning parameters in both pharmacological and natural models of memory impairments are also intriguing. The possible relevance of these findings to diseases such as age-related memory disorders, Alzheimer's disease and ADHD is certainly worthy of consideration and awaits confirmation from clinical trials. Interestingly, tacrine, which is used successfully in some patients with Alzheimer's disease, is more active as an inhibitor of histamine-N-methyltransferase than acetylcholine esterase both *in vitro* and *in vivo*^{75,76}. In view of this effect

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on histamine metabolism, the combination of tacrine and an H₃ receptor antagonist could be beneficial in these conditions⁷⁵.

The highly localized CNS distribution of the H₃ receptor⁷⁷ suggests that limited peripheral side-effects will be seen after treatment with an H₃ receptor antagonist. Furthermore, peripheral histamine-mediated tone is normally minimal, and the H₃ receptor thus is mainly quiescent under normal physiological conditions. Indeed, no cardiovascular⁸ or neuroendocrine effects⁷⁸ have been reported after treatment with H₃ receptor antagonists.

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Chemical names

- AQ0145: N-(1-adamantyl)-4-(4(5)-imidazolyl)piperidine-1-methaneimine
- BP294: (R)-N-(2-hydroxy- α -phenylphenyl)methylidene)-2-(4(5)-imidazolyl)-1-methylethylamine
- FUB181: 4(5)-[3-[3-(4-chlorophenyl)propoxy]propyl]imidazole
- FUB307: (R)-N-[(5-fluoro-2-hydroxy- α -(2-pyrrolyl)phenyl)methylidene]-2-(4(5)-imidazolyl)-1-methylcethylamine
- GR175737: 3-(4-chlorophenylmethyl)-5-[2-(4(5)-imidazolyl)ethyl]-1,2,4-oxadiazole
- CT2016: 1-(5-cyclohexylpentanoyl)-4-(4(5)-imidazolyl)piperidine
- GT2227: 4(5)-(6-cyclohexyl-3-hexen-1-yl)imidazole
- SKF91606: 4-(4(5)-imidazolyl)butyramidine
- UCL1199: 2-[2-(4(5)-imidazolyl)ethylthio]-5-nitropyridine